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EXAMINER	
FORMAN, BETTY J	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/628,472	WOLBER ET AL.
	Examiner	Art Unit
	BJ Forman	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *03/03* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

FINAL ACTION

1. This action is in response to papers filed 10 February 2003 in which claim 1 was amended. The amendments have been thoroughly reviewed and entered. The previous objection to the specification and rejections under 35 U.S.C. 112, first paragraph in the Office Action dated 1 November 2002 are maintained. The previous rejections under 35 U.S.C. 102(e) and 35 U.S.C. 103(a) are withdrawn in view of the amendments. All of the arguments have been thoroughly reviewed and are discussed below as they apply to the maintained rejections. Arguments regarding the withdrawn rejections are deemed moot in view of the amendments, withdrawn rejections and new grounds for rejection.

New grounds for rejection necessitated by the Amendments and the Information Disclosure Statement filed 11 March 2003 are discussed.

Claims 1-15 are under prosecution.

Specification

2. The amendment filed 3 September 2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendments to Claims 1 and 5 (from which claims 2-4 and 6-15 depend) adds the limitation "a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence" but the specification as originally filed does not provide support for the new limitations.

Applicant points to page 18, steps 3 and 4 for support for the new limitations. However, this merely teaches a transcription mixture is added to the hybridization chamber (step 3) and the transcription mixtures are removed and concentrated (step 4). This passage does not teach a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence as newly claimed. Therefore, the amendments add subject matter not supported by the original disclosure.

Applicant is required to cancel the new matter in the reply to this Office Action.

Response to Arguments

3. Applicant argues that the recitation "solution phase product" does not introduce new matter into the specification because the specification at page 10, line 25 and at page 18, lines 2-13 provides support for the recitation.

The argument has been considered but is not found persuasive because the passages cited by applicant are not commensurate in scope within the context of the claims. The claims are drawn to a method for producing a mixture of nucleic acids comprising providing an array of single-stranded probes, hybridizing nucleic acids complementary to the arrayed nucleic acids to form overhang duplexes and subjecting the duplexes to primer extension. The cited passages refer to polymerase chain reaction (PCR), strand displacement amplification (SDA) and transcription. Regarding, PCR and SDA, Applicant cannot rely on the teaching of PCR and SDA for support of solution phase product because both PCR and SDA require two primers. In contrast to PCR and SDA, the instantly claimed method utilizes a single primer. As such, the PCR and SDA taught in the specification cannot provide support for the instant claims. Regarding transcription, Applicant cannot rely on the teaching of transcription for support of solution phase product because transcription conflicts with the instantly claimed primer extension because polymerase enzymes do not require primers as evidenced by the instant specification which specifically teaches that polymerase enzymes are primer independent.

> i.e. the complementary strand of the T-7 promoter portion of the oligonucleotide on the surface. The purpose of this treatment was to produce a double-stranded T-7 promoter, which is necessary for T-7 RNA polymerase activity (note that a double-stranded template strand is not necessary; a 5'-overhanging single-stranded template is known to be sufficient). (page 18, lines 1-5).

Therefore, the recitation "solution phase product" cannot find support in the cited passages because 1) the instant claims require a single primer and primer extension; 2) PCR and SDA require two primers; 3) transcription is primer independent; and 4) the claims are not limited to PCR, SDA or transcription.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To the extent that the claimed methods are not described in the instant disclosure, claims 1-15 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject

matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

The recitation "that produces a solution phase product comprising a mixture of nucleic acids of differing sequence " is added to the newly amended independent Claims 1 and 5 (from which Claims 2-4 and 6-15 depend). However, the specification fails to define or provide any disclosure to support such claim recitation. Applicant points to page 18, steps 3 and 4 for support for the new limitations. However, this passage merely teaches a transcription mixture is added to the hybridization chamber (step 3) and the transcription mixtures are removed and concentrated (step 4). This passage does not teach a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence as newly claimed. Therefore, the specification fails to support the newly added amendments.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

Response to Arguments

6. Applicant argues that the recitation "solution phase product" does not introduce new matter into the specification because the specification at page 10, line 25 and at page 18, lines 2-13 provides support for the recitation.

The argument has been considered but is not found persuasive because the passages cited by applicant are not commensurate in scope within the context of the claims. The claims are drawn to a method for producing a mixture of nucleic acids comprising providing an array of single-stranded probes, hybridizing nucleic acids complementary to the arrayed nucleic acids to form overhang duplexes and subjecting the duplexes to primer extension. The cited passages refer to polymerase chain reaction (PCR), strand displacement amplification (SDA) and transcription. Regarding, PCR and SDA, Applicant cannot rely on the teaching of PCR and SDA for support of solution phase product because both PCR and SDA require two primers. In contrast to PCR and SDA, the instantly claimed method utilizes a single primer. As such, the PCR and SDA taught in the specification cannot provide support for the instant claims. Regarding transcription, Applicant cannot rely on the teaching of transcription for support of solution phase product because transcription conflicts with the instantly claimed primer extension because polymerase enzymes do not require primers as evidenced by the instant specification which specifically teaches that polymerase enzymes are primer independent.

> i.e. the complementary strand of the T-7 promoter portion of the oligonucleotide on the surface. The purpose of this treatment was to produce a double-stranded T-7 promoter, which is necessary for T-7 RNA polymerase activity (note that a double-stranded template strand is not necessary; a 5'-overhanging single-stranded template is known to be sufficient). (page 18, lines 1-5).

Therefore, the recitation "solution phase product" cannot find support in the cited passages because 1) the instant claims require a single primer and primer extension; 2) PCR and SDA require two primers; 3) transcription is primer independent; and 4) the claims are not limited to PCR, SDA or transcription.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Wolber et al (U.S. Patent No. 6,235,483, filed 31 January 2000).

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding Claim 1, Wolber et al disclose a method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. poly A) and a complement variable domain (i.e. coding sequences); hybridizing nucleic acids complementary to the constant domain with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region

overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (Columns 6 and 13).

Regarding Claim 2, Wolber et al disclose the method wherein the nucleic acid mixture comprises deoxyriobologonucleotides (Column 6).

Regarding Claim 3, Wolber et al disclose the method wherein the constant domain comprise at least one domain selected from a linker domain, a functional domain and a recognition domain (Columns 5-6).

Regarding Claim 4, Wolber et al disclose the method wherein step (c) comprises linear PCR (Column 6).

Regarding Claim 5, Wolber et al disclose a method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. constant priming sequence) and a complement variable domain (i.e. flanking sequences); hybridizing nucleic acids complementary to the constant domain with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (Columns 6 and 13) wherein the probe comprises: 3' linker- recognition domain-functional domain-complement domain and the complementary_nucleic acids comprise a complement of the recognition domain and complement of the functional domain (Columns 5-6)

Regarding Claim 6, Wolber et al teach the method wherein the linker domain ranges in length from about 0 to 10 bases (Columns 5-6).

Regarding Claim 7, Wolber et al teach the method wherein the functional domain is an RNA polymerase promoter domain (Column 5-6).

Regarding Claim 8, Wolber et al teach the method wherein the recognition domain is recognized by a restriction endonuclease (Column 7, lines 21-44).

Regarding Claim 9, Wolber et al teach the method the primer extension step comprises linear PCR or in vitro transcription (Columns 5-6).

Regarding Claim 10, Wolber et al disclose a method for producing a mixture of nucleic acids comprising: generating a mixture of nucleic acids according to Claim 1 and employing the mixture as primers in a target generation step whereby a population of nucleic acids is produced (Column 8).

Regarding Claim 11, Wolber et al. teach the similar method wherein the target generation step comprises template driven primer extension (Column 8).

Regarding Claim 12, Wolber et al. teach the similar method wherein said target generation step produces labeled target nucleic acids (Column 8).

Regarding Claim 13, Wolber et al. teach the similar method of generating a set of target nucleic acids according to the method of Claim 10; and further contacting said set of nucleic acids with nucleic acids under hybridizing condition; and detecting the presence of target nucleic acids hybridized to nucleic acids (Column 8).

Regarding Claim 14, Wolber et al. teach the similar method of Claim 13 wherein the nucleic acids are labeled (Column 8).

Regarding Claim 15, Wolber et al teach their method wherein following hybridization and/or detection, unbound target molecules are removed (Column 8-10).

9. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577).

Regarding Claim 1, Bulyk et al disclose a method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. constant priming sequence) and a complement variable domain (i.e. flanking sequences); hybridizing nucleic acids complementary to the constant domain with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (page 576, right column-page 577, left column).

Regarding Claim 2, Bulyk et al disclose the method wherein the nucleic acid mixture comprises deoxyriobologonucleotides (page 573, right column first full paragraph).

Regarding Claim 3, Bulyk et al disclose the method wherein the constant domain comprise at least one domain selected from a linker domain, a functional domain and a recognition domain (page 574, Fig. 1).

Regarding Claim 4, Bulyk et al disclose the method wherein step (c) comprises linear PCR i.e. utilizes a single primer for priming only the 3' end of the immobilized nucleic acids (page 574, Fig. 1).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 5-6 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577).

Regarding Claim 5, Bulyk et al disclose a method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. constant priming sequence) and a complement variable domain (i.e. flanking sequences); hybridizing nucleic acids complementary to the constant domain with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (page 576, right column-page 577, left column) wherein the probe comprises: 3' linker-recognition domain (constant priming sequence)-functional domain (proximal flanking

sequence)-(distal flanking sequence) and the complementary nucleic acids comprise a sequence which hybridizes to the probe nucleic acid (Abstract). Bulyk et al teach their probes comprise sequences to facilitate primer binding and extension (Abstract) which clearly suggests that their probes comprise both a functional and recognition domains, but they do not specifically teach nucleic acids comprise both functional and recognition domains. However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the functional and recognition domain suggestion of Bulyk et al the their probes of their array designed for amplification of template-specific sequences for the expected benefit of facilitating the amplification and purification of template-specific sequences as suggested by Bulyk et al (Abstract).

Regarding Claim 6, Bulyk et al teach the method wherein the linker domain ranges in length from about 0 to 10 bases i.e. HEG linker (page 574, left column, lines 1-4, Fig. 1 and page 576, right column, first full paragraph).

Regarding Claim 8, Bulyk et al teach the method wherein the recognition domain is recognized by a restriction endonuclease (page 574, left column first full paragraph).

Regarding Claim 9, Bulyk et al teach the method the primer extension step comprises in vitro transcription i.e. the functional domain provides a polymerase binding region to which the DNA polymerase binds to initiate transcription (page 575, right column, third full paragraph).

12. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577) as applied to Claim 5 above and further in view of Dattagupta (U.S. Patent No. 5,215,899, issued 1 June 1993).

Regarding Claim 7, Regarding Claim 5, Bulyk et al disclose a method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. constant priming sequence) and a complement variable domain (i.e. flanking sequences); hybridizing nucleic acids complementary to the constant domain with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (page 576, right column-page 577, left column) wherein the probe comprises: 3' linker- recognition domain (constant priming sequence)-functional domain (proximal flanking sequence)-(distal flanking sequence) and the complementary nucleic acids comprise a sequence which hybridizes to the probe nucleic acid (Abstract). Bulyk et al teach their probes comprise sequences to facilitate primer binding and extension (Abstract) which clearly suggests that their probes comprise both a functional and recognition domains, but they do not teach an RNA polymerase promoter domain. However, RNA polymerase were well know in the art at the time the claimed invention was made as taught by Dattagupta who teaches a similar method for producing a mixture of distinct deoxyribo-oligonucleotide wherein the a plurality of single-stranded probes having the formula: A-B-C-5' wherein is A recognition domain, B is functional domain and C is a variable domain. The method comprising contacting the probes with nucleic acids having the formula A' B'; and subjecting the overhang duplex to primer extension to thereby produce a plurality of nucleic acids (Column 4, lines 27-53) wherein the functional + recognition domains function to recognize the target sequence and transcription initiation site wherein the functional domain is an RNA polymerase promoter domain wherein binding of the polymerase initiates RNA transcription (Abstract) (Column 5,

lines 22-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the polymerase of Bulyk et al with RNA polymerase taught by Dattagupta et al. whereby transcription and amplification are performed without using the time consuming and cumbersome thermocycling of PCR for the obvious benefits of simplified transcription and amplification as taught by Dattagupta et al. (Column 3, lines 58-67).

13. Claims 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577) in view of Cantor et al (U.S. Patent No. 5,795,714, issued August 18, 1998).

Regarding Claim 10, Bulyk et al disclose a method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. constant priming sequence) and a complement variable domain (i.e. flanking sequences); hybridizing nucleic acids complementary to the constant domain with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (page 576, right column-page 577, left column) wherein the mixture of nucleic acids are used to produce a population of target molecules (page 577, left column) but they do not teach the mixture of nucleic acids are employed as primers to generate a population of target nucleic

acids. However, Cantor et al. teach a similar method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids, contacting said array with nucleic acids complementary to said constant domain under hybridization conditions whereby a template array of overhang comprising duplex nucleic acids is produced, wherein each overhang comprising duplex of said array comprises a double-stranded region and a single-stranded variable region overhang; subjecting said template array to primer extension to produce a mixture of nucleic acids (Column 13, line 41-Column 14, line 22) and further comprising; employing said mixture as primers in a target generation step in which target nucleic acids are produced i.e. to create duplicate arrays (Column 4, lines 48-50) wherein the nucleic acids are RNAs (Column 6, lines 43-47). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Bulyk et al by employing the mixture of nucleic acids as primers to thereby duplicate template arrays as taught by Cantor et al (Column 4, lines 48-65).

Regarding Claim 11, Cantor et al. teach the similar method wherein the target generation step comprises template driven primer extension (Column 4, lines 57-58).

Regarding Claim 12, Cantor et al. teach the similar method wherein said target generation step produces labeled target nucleic acids (Column 9, lines 28-50).

Regarding Claim 13, Cantor et al. teach the similar method of generating a set of target nucleic acids according to the method of Claim 10; and further contacting said set of nucleic acids with nucleic acids under hybridizing condition; and detecting the presence of target nucleic acids hybridized to nucleic acids i.e. the generated nucleic acids are free in solution and hybridized to other nucleic acids for detecting the nucleic acids (Column 4, lines 48-65). Cantor et al. do not teach the nucleic acids in solution are contacted with an array of probes. However, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the hybridization of Cantor et al. by hybridizing the generated nucleic acids to probes on an array to thereby detect the generated sequences using positional

screening for the expected benefit of rapidly and accurately the sequence of the nucleic acid generated as taught by Cantor et al. (Column 4, lines 11-15).

Regarding Claim 14, Cantor et al. teach the similar method of Claim 13 wherein the nucleic acids are labeled (Column 9, lines 1-27).

Regarding Claim 15, Bulyk et al teach their method wherein following hybridization and/or detection, unbound target molecules are removed (page 574, left column, first full paragraph). Cantor et al. teach the similar method of Claim 13 for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids, contacting said array with nucleic acids complementary to said constant domain under hybridization conditions whereby a template array of overhang comprising duplex nucleic acids is produced, wherein each overhang comprising duplex of said array comprises a double-stranded region and a single-stranded variable region overhang; subjecting said template array to primer extension to produce a mixture of nucleic acids (Column 13, line 41-Column 14, line 22) but they do not specifically teach said method further comprises washing unbound target away from the surface of the array. However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the know washing step to remove unbound nucleic acids to the methods of Bulyk et al and Cantor et al. washing unbound target from the surface of the array for the obvious benefit of eliminating non-specific sequences and reducing background hybridizations.

14. Claims 1-6, 8-9 are rejected under 35 U.S.C. 103(e) as being unpatentable over Lipshutz et al (U.S. Patent No. 6,280,950 B1, filed 10 March 1997) in view of Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577).

Regarding Claim 1, Lipshutz et al disclose a method for producing a mixture of nucleic acids (Column 2, lines 16-37) comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. 3' terminal sequence) and a complement variable domain (i.e. unique central sequences); hybridizing nucleic acids complementary to the constant domain (i.e. primers) with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (Column 2, lines 16-37; Column 21, line 34-Column 23, line 21; and Fig. 1). Lipshutz et al teach the method wherein the 5' sequence of the probe is common to all templates whereby the template is amplified using 5' and 3' primers. While they do not teach the 5' end is variable, Bulyk et al teach a similar method wherein the 5' sequence of the probe is variable and whereby template is amplified via primer extension using a single primer to thereby replicate templates of long length with accuracy and efficiency (Abstract and page 573, right column first full paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 5' and 3' constant region template of Lipshutz et al with the 3' constant region and 5' variable region template of Bulyk et al wherein the template is amplified accurately and efficiently using a single primer. One of ordinary skill in the art would have been motivated to combine the teachings of Bulyk et al and Lipshutz et al based on the teachings of Bulyk et al

to thereby efficiently and accurately produce the desired mixture of nucleic acids as taught by Bulyk et al (Abstract and page 573, right column first full paragraph).

Regarding Claim 2, Lipshutz et al disclose the method wherein the mixture of nucleic acids is a mixture of DNA (i.e. the primer is extended via PCR using Taq DNA polymerase, Column 22,lines 21-27).

Regarding Claim 3, Lipshutz et al disclose the method wherein the constant domain comprises at least one domain selected from the group consisting of a linker domain, a functional domain and a recognition domain (Column 16, lines 16-46 and Column 21, lines 5-22).

Regarding Claim 4, Lipshutz et al teach the method the primer extension step comprises in vitro transcription i.e. the functional domain provides a polymerase binding region to which the polymerase binds to initiate transcription (Column 15, lines 45-54)

Regarding Claim 5, Lipshutz et al teach a method for producing a mixture of a plurality of distinct deoxyribo-oligonucleotides of differing sequence wherein each oligonucleotide comprises a different variable region (Column 2, lines 16-37) comprising: providing an array of a plurality of surface immobilized single stranded probes wherein each probe on the array comprises a constant domain (i.e. 3' terminal sequence) and a complement variable domain (i.e. unique central sequences) wherein the constant domain comprises ancillary sequences (Column 11, lines 17-20); contacting the array under hybridizing conditions with a population of nucleic acids complementary to the constant domain whereby an array of overhang duplex nucleic acids is produced; subjecting the duplex nucleic acids to primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array to produce a mixture of a plurality of distinct oligonucleotides of differing sequence each comprising a different variable domain (Column 2, lines 16-37; Column 21, line 34-Column 23, line 21; and Fig. 1). Lipshutz et al teach the probes are linked to a solid support via a linker (Column 21, lines 5-8) and further

comprise a constant domain (i.e. 3' terminal sequence) which comprises ancillary sequences (Column 11, lines 17-20) wherein the ancillary sequences facilitate amplification and /or purification. Specifically, their functional domains facilitate amplification (e.g. common primer binding domain; Column 15, line 35- 67) and their recognition domains facilitate purification (e.g. restriction enzyme and sequence-specific recognition domains; Column 16, lines 16-46). Lipshutz et al teach their probes comprise ancillary sequences to facilitate amplification and purification which clearly suggests that their probes comprise both a functional and recognition domains, but they do not specifically teach probes comprise both functional and recognition domains having the formula L-R+F-cV-5'. However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the functional and recognition domain suggestion of Lipshutz et al the their probes of their array designed for amplification of template-specific sequences for the expected benefit of facilitating the amplification and purification of template-specific sequences as suggested by Lipshutz et al (Column 11, lines 17-20).

Regarding Claim 6, Lipshutz et al teach the method wherein the linker domain ranges in length from about 0 to 10 bases e.g. terminal hydroxyl (Column 21, lines 5-15).

Regarding Claim 8, Lipshutz et al teach the method wherein the recognition domain is recognized by a restriction endonuclease (Column 16, lines 32-37).

Regarding Claim 9, Lipshutz et al teach the method the primer extension step comprises in vitro transcription i.e. the functional domain provides a polymerase binding region to which the polymerase binds to initiate transcription (Column 15, lines 45-54).

15. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lipshutz et al (U.S. Patent No. 6,280,950 B1, filed 10 March 1997)) and Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577) as applied to Claim 5 above and further in view of Dattagupta (U.S. Patent No. 5,215,899, issued 1 June 1993).

Regarding Claim 7, Lipshutz et al teach a method for producing a mixture of a plurality of distinct deoxyribo-oligonucleotides of differing sequence wherein each oligonucleotide comprises a different variable region (Column 2, lines 16-37) comprising: providing an array of a plurality of surface immobilized single stranded probes wherein each probe on the array comprises a constant domain (i.e. 3' terminal sequence) and a complement variable domain (i.e. unique central sequences) wherein the constant domain comprises ancillary sequences (Column 11, lines 17-20); contacting the array under hybridizing conditions with a population of nucleic acids complementary to the constant domain whereby an array of overhang duplex nucleic acids is produced; subjecting the duplex nucleic acids to primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array to produce a mixture of a plurality of distinct oligonucleotides of differing sequence each comprising a different variable domain (Column 2, lines 16-37; Column 21, line 34-Column 23, line 21; and Fig. 1) wherein the functional domain provides a polymerase binding region for polymerase binding and transcription initiation (Column 15, lines 45-54) but they do not teach an RNA polymerase promoter domain. However, RNA polymerase were well know in the art at the time the claimed invention was made as taught by Dattagupta who teaches a similar method for producing a mixture of distinct deoxyribo-oligonucleotide wherein the a plurality of single-stranded probes having the formula: A-B-C-5' wherein is A recognition domain, B is functional domain and C is a variable domain. The method comprising contacting the probes with nucleic acids having the formula A' B'; and subjecting the overhang duplex to primer extension to thereby produce a

plurality of nucleic acids (Column 4, lines 27-53) wherein the functional + recognition domains function to recognize the target sequence and transcription initiation site wherein the functional domain is an RNA polymerase promoter domain wherein binding of the polymerase initiates RNA transcription (Abstract) (Column 5, lines 22-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the polymerase of Lipshutz et al with RNA polymerase taught by Dattagupta et al. whereby transcription and amplification are performed without using the time consuming and cumbersome thermocycling of PCR for the obvious benefits of simplified transcription and amplification as taught by Dattagupta et al. (Column 3, lines 58-67).

16. Claims 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipshutz et al (U.S. Patent No. 6,280,950 B1, filed 10 March 1997)) in view of Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577) and Cantor et al (U.S. Patent No. 5,795,714, issued August 18, 1998).

Regarding Claim 10, Lipshutz et al teach a method for producing a mixture of nucleic acids according to Claim 1 comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. 3' terminal sequence) and a complement variable domain (i.e. unique central sequences); hybridizing nucleic acids complementary to the constant domain (i.e. primers) with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-

stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (Column 2, lines 16-37; Column 21, line 34-Column 23, line 21; and Fig. 1) wherein the mixture of nucleic acids are used to produce a population of target molecules (Column 9, line 30-41). Lipshutz et al teach the method wherein the 5' sequence of the probe is common to all templates whereby the template is amplified using 5' and 3' primers. While they do not teach the 5' end is variable, Bulyk et al teach a similar method wherein the 5' sequence of the probe is variable and whereby template is amplified via primer extension using a single primer to thereby replicate templates of long length with accuracy and efficiency (Abstract and page 573, right column first full paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 5' and 3' constant region template of Lipshutz et al with the 3' constant region and 5' variable region template of Bulyk et al wherein the template is amplified accurately and efficiently using a single primer. One of ordinary skill in the art would have been motivated to combine the teachings of Bulyk et al and Lipshutz et al based on the teachings of Bulyk et al to thereby efficiently and accurately produce the desired mixture of nucleic acids as taught by Bulyk et al (Abstract and page 573, right column first full paragraph).

Lipshutz et al do not teach the mixture of nucleic acids are employed as primers to generate the population. However, Cantor et al. teach a similar method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids, contacting said array with nucleic acids complementary to said constant domain under hybridization conditions whereby a template array of overhang comprising duplex nucleic acids is produced, wherein each overhang comprising duplex of said array comprises a double-stranded region and a single-stranded variable region overhang; subjecting said

template array to primer extension to produce a mixture of nucleic acids (Column 13, line 41-Column 14, line 22) and further comprising; employing said mixture as primers in a target generation step in which target nucleic acids are produced i.e. to create duplicate arrays (Column 4, lines 48-50) wherein the nucleic acids are RNAs (Column 6, lines 43-47). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Lipshutz et al by employing the mixture of nucleic acids as primers to thereby duplicate template arrays as taught by Cantor et al (Column 4, lines 48-65).

Regarding Claim 11, Cantor et al. teach the similar method wherein the target generation step comprises template driven primer extension (Column 4, lines 57-58).

Regarding Claim 12, Cantor et al. teach the similar method wherein said target generation step produces labeled target nucleic acids (Column 9, lines 28-50).

Regarding Claim 13, Cantor et al. teach the similar method of generating a set of target nucleic acids according to the method of Claim 10; and further contacting said set of nucleic acids with nucleic acids under hybridizing condition; and detecting the presence of target nucleic acids hybridized to nucleic acids i.e. the generated nucleic acids are free in solution and hybridized to other nucleic acids for detecting the nucleic acids (Column 4, lines 48-65). Cantor et al. do not teach the nucleic acids in solution are contacted with an array of probes. However, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the hybridization of Cantor et al. by hybridizing the generated nucleic acids to probes on an array to thereby detect the generated sequences using positional screening for the expected benefit of rapidly and accurately the sequence of the nucleic acid generated as taught by Cantor et al. (Column 4, lines 11-15).

Regarding Claim 14, Cantor et al. teach the similar method of Claim 13 wherein the nucleic acids are labeled (Column 9, lines 1-27).

Regarding Claim 15, Lipshutz et al teach their method wherein following hybridization and/or detection, unbound target molecules are removed by washing (e.g. Column 9 and 36-39). Cantor et al. teach the similar method of Claim 13 for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids, contacting said array with nucleic acids complementary to said constant domain under hybridization conditions whereby a template array of overhang comprising duplex nucleic acids is produced, wherein each overhang comprising duplex of said array comprises a double-stranded region and a single-stranded variable region overhang; subjecting said template array to primer extension to produce a mixture of nucleic acids (Column 13, line 41-Column 14, line 22) but they do not specifically teach said method further comprises washing unbound target away from the surface of the array. However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the know washing step to remove unbound nucleic acids to the methods of Lipshutz et al and Cantor et al. washing unbound target from the surface of the array for the obvious benefit of eliminating non-specific sequences and reducing background hybridizations.

Prior Art

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Uhlen (U.S. Patent No. 5,405,746, issued 11 April 1995) teach a method for producing nucleic acids comprising primers having constant and variable domains, extending the primers and separating the nucleic acids (Column 6, line 42-Column 7, line 25 and Fig. 1).

Dattagupta (U.S. Patent No. 4,734,363, issued 29 March 1988) teach a method for producing nucleic acids comprising primers having constant and variable domains, extending the primers and separating the nucleic acids (Column 2, line 19-Column 3, line 34 and Fig. 1).

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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Patent Examiner
Art Unit: 1634
May 9, 2003

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